The Epidemiology of Bacillary Angiomatosis and Bacillary Peliosis

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Objective.—To determine environmental risk factors for bacillary angiomatosis—bacillary peliosis (BAP), and to confirm infection with Rochalimaea species.

Design.—Case-control study.

Setting.—Community and university hospitals and clinics.

Patients.—Case patients (N=48) had biopsy-confirmed BAP. Controls (N=94) were matched to patients by institution and by human immunodeficiency virus (HIV) serological status.

Main Outcome Measures.—Clinical information was obtained from medical records. Subjects were queried about environmental exposures. Univariate odds ratios (ORs) with 95% confidence intervals (CIs) were determined. Bivariate analyses were performed on variables associated with disease by univariate analysis. DNA from 22 available case-patient tissues and from 22 control tissues was amplified with the polymerase chain reaction (PCR) using primers designed to detect Rochalimaea species.

Results.—We identified five HIV-negative, immunocompetent case patients; one HIV-negative, immunodeficient case patient; and 42 HIV-positive case patients. There were no significant differences between case patients and controls by race, sex, age, or risk factors for HIV infection. Owning a cat (OR, 2.8; CI, 1.4 to 5.8) and history of a recent cat lick (OR, 1.95; CI, 1.0 to 3.8), cat scratch (OR, 3.7; CI, 1.7 to 8.0), or cat bite (OR, 3.9; CI, 1.8 to 8.9) were associated with disease in the univariate analysis. In bivariate analyses, only the variables representing traumatic contact with a cat (bite or scratch) remained associated with disease. No other environmental exposure was associated with disease. The PCR amplified a DNA fragment of the size expected for Rochalimaea species in all 22 case-patient tissue specimens.

Conclusions.—These data suggest that BAP is a new zoonosis associated with both traumatic exposure to cats and infection with Rochalimaea species or a closely related organism.

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Bacillary angiomatosis (BA) was first described in human immunodeficiency virus (HIV)-infected patients who presented with subcutaneous and cutaneous vascular lesions mimicking Kaposi's sarcoma.12 Bacillary angiomatosis derives its name from the vascular proliferation seen on histologic examination of affected tissues (including skin, bone, lymph node, and brain) and from the presence of numerous bacillary organisms demonstrable on Warthin-Starry silver staining or on electron microscopy.13 These bacilli are also visible in parenchymal vascular lesions of bacillary peliosis of the liver (bacillary peliosis hepatis) and spleen.9,10 Because BA and bacillary peliosis represent different manifestations of the same infection, the term bacillary angiomatosis–bacillary peliosis (BAP) will be used to refer to this disease process.

Initially, several observations suggested that BAP was caused by infection with the cat-scratch disease (CSD) bacillus, Warthin-Starry staining and electron microscopy of tissue sections from patients with BAP revealed bacillary organisms resembling those seen in patients with classic CSD,17,41 and several case reports of BAP suggested that BAP might represent disseminated CSD in the immunocompromised host,9,10 In addition, marked similarities were noted, both clinically and histologically, between the cutaneous lesions of BA and verruga peruana (a late manifestation of infection with Bartonella bacilliformis).4 However, recent molecular biologic and microbiologic investigations confirm that at least two organisms, Rochalimaea henselae,18 and Rochalimaea quintana,18,19 can cause BA, both of which are distinct from Afipia felis (formerly the CSD bacillus) and Bacillus bacilliformis.15-29

We conducted a case-control study to identify risk factors for BAP and to test the hypothesis that our case-patients with BAP were infected with Rochalimaea species or a closely related organism. Because of the numerous anecdotal reports suggesting that cat exposure preceded symptoms of BAP,18,25,30 we queried subjects in detail regarding a wide range of animal exposures, including physical and sexual contact, and questioned pet owners about specific interactions with their pets. In addition, because cutaneous lesions of BA resemble those caused by infection with B
bacilli, and because this organism is found only in South America and is transmitted by an insect vector, we queried subjects in detail regarding foreign travel and exposures to imported South American goods (including cocaine) and to insects. We also explored plant, soil, water, and traumatic exposures because CSD has been reported following skin trauma from wood splinters, fish hooks, pins, thorns, and porcupine quills in the absence of cat contact. Finally, we used the polymerase chain reaction (PCR) to test tissue specimens from case-patients for the presence of Rochalimaea species DNA.

METHODS

Case Definition

We defined a case as an illness in a patient with histologically confirmed lesions of BAP. Histologically confirmed BA lesions showed (1) a lobular proliferation of small, round blood vessels with plump endothelial cells (with or without cytologic atypia) protruding into the vascular lumen; (2) necrosis present within the centers of vascular lobules; (3) a mixed inflammatory cell infiltrate with neutrophils and leukocytes; and (4) granular amphiphilic interstitial material revealing bacilli on silver staining (eg, Warthin-Starry) or electron microscopy or both. Histologically confirmed parenchymal lesions showed (1) dilated capillaries or multiple dilated, blood-filled spaces or (2) a myxoid stroma containing a mixture of inflammatory cells and clumps of granular amphiphilic material (revealing bacilli on silver staining or electron microscopy) or both.

Study Participants

All patients 18 years of age or older with biopsy-confirmed BAP were eligible for enrollment as case patients. Case patients were identified by reviewing pathology records at the University of California, San Francisco, Hospitals and Clinics. In addition, both University of California, San Francisco, and San Francisco Bay Area community clinicians and pathologists were asked to notify the principal investigator (J.W.T.) if they identified a patient with BAP. Case patients identified from outside the San Francisco Bay Area were recruited from clinicians and pathologists who were informed of the study and had identified a patient with BAP. Histologic tissue specimens from 48 case patients were reviewed by a pathologist familiar with BAP (P.E.L.) to confirm eligibility. Surrogates (relatives or a significant other) answered questions about case patients who had died or had dementia.

Patients 18 years of age or older without a prior history of BAP were eligible for enrollment as controls. Health care providers identified two controls per BAP case, matched to case patients by HIV serological status and clinical institution. Controls were selected from the same primary physician outpatient schedule book (registry, log, or list) as case patients. Potential controls were asked to participate by their health care provider. A copy of the schedule log used to identify controls was maintained to verify that each control was selected as close as possible to the same day in which the BAP case patient or surrogate was interviewed and to document the reasons for those declining participation. Telephone contact between a study investigator and eligible controls required, on average, calling three eligible controls per case. Before moving down the schedule log to the next eligible control, an average of two telephone calls for each eligible control was made. Once reached, only seven eligible controls declined to participate, and 94 controls were enrolled. The study was approved by the Committee for Human Research, University of California, San Francisco.

Questionnaire

Using a standard questionnaire, three study investigators questioned consenting case patients and controls (either in person or by telephone) about demographic characteristics, medical history, and recent exposures to water, soil, plants, and animals. All subjects with an animal exposure, regardless of species (dog, cat, bird, rodent, and so forth), were queried using the same set of questions. For pet owners with one or more pets of the same type, data were collected on as many as three household pets of the same type as well as on pet contact outside the home. Case patients were asked about exposures in the 6 months before BAP tissue diagnosis. Controls were asked about exposures in the 6 months before enrollment. Clinical information was extracted from the hospital and clinic charts of case patients and controls.

Analyses

A preliminary analysis of the data from the first 21 case patients enrolled suggested a possible link between disease and exposure to cats. To investigate this finding further, an addendum questionnaire with more details about exposure was administered to the previously enrolled, living case patients (n=1) and matched controls (n=2) who could be located, and to all subsequently enrolled case patients (n=27) and controls (n=52). Detailed information regarding cat exposure among those owning a cat was requested for the 6 months before diagnosis (case patients) or enrollment (controls), and information on specific insect bites and terrain exposures was requested for the 1-year period prior to study enrollment.

After the collection of data on the first 35 case patients in this study, it was suspected that a number of case patients had been told initially by their physicians that they had CSD, raising the possibility that recall bias regarding prior or current cat exposure may have been introduced. Therefore, at the time of enrollment of the next 13 case patients, all patients were queried, before administering the questionnaire regarding all possible diagnoses given to them by their physician.

Several matched subanalyses were conducted on the data by excluding surrogate interviews and excluding case patients interviewed more than 6 months following their BAP tissue diagnosis to investigate the effect of these responses on the overall results. When necessary, subanalyses were conducted on unmatched data to maintain statistical power in the setting of a diminished number of matched case and control sets for these analyses. Unmatched analyses included a comparison of cat exposures among case patients and controls who owned a cat or cats and an analysis that compared cat exposures between case patients and controls who had never been given a diagnosis of CSD.

Statistical Methods

The Mann-Whitney U test was used to assess differences between two groups, and matched univariate odds ratios (ORs) were calculated by the Mantel-Haenszel method using Epi-Info, a statistical software package. Unmatched univariate ORs were calculated using Epi-Info on two subanalyses of the data. For these unmatched analyses, P values were calculated using the Mantel-Haenszel method or the two-tailed Fisher’s Exact Test (for analyses with small numbers of observations). A bivariate matched analysis was conducted on cat exposure variables with significant univariate ORs using the PHREG procedure on SAS, a statistical software package.

Tissue Studies

Biopsied tissue specimens were requested from the clinicians and pathologists who identified 48 case patients. Following sectioning and Warthin-Starry staining of submitted tissue samples, 22 tissue specimens containing
Table 1.—Personal and Behavioral Characteristics of Study Participants*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Patients (N=48)</th>
<th>Controls (N=94)</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>38.5</td>
<td>37.0</td>
<td>.49†</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>87.5</td>
<td>89.4</td>
<td>.69</td>
</tr>
<tr>
<td>Race, % white</td>
<td>90.0</td>
<td>95.0</td>
<td>.71</td>
</tr>
<tr>
<td>Ethnicity, % non-Hispanic</td>
<td>79.2</td>
<td>79.8</td>
<td>.94</td>
</tr>
<tr>
<td>Annual income, % &lt;$10'000</td>
<td>23.4</td>
<td>18.3</td>
<td>.57</td>
</tr>
<tr>
<td>Education, % high school or less</td>
<td>37.5</td>
<td>35.1</td>
<td>.85</td>
</tr>
<tr>
<td>Housing, % apartment living</td>
<td>50.0</td>
<td>47.9</td>
<td>.95</td>
</tr>
<tr>
<td>AIDS diagnosis, % with AIDS</td>
<td>50.0</td>
<td>46.8</td>
<td>.74</td>
</tr>
<tr>
<td>Kaposi's sarcoma, %</td>
<td>25.0</td>
<td>12.0</td>
<td>.07</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia, %</td>
<td>27.1</td>
<td>26.6</td>
<td>.95</td>
</tr>
<tr>
<td>Times hospitalized, % mean</td>
<td>0.9</td>
<td>1.2</td>
<td>.07†</td>
</tr>
<tr>
<td>Total days hospitalized, % mean</td>
<td>9.7</td>
<td>12.2</td>
<td>.04</td>
</tr>
<tr>
<td>Homosexual male, %</td>
<td>87.5</td>
<td>89.4</td>
<td>.50</td>
</tr>
<tr>
<td>Intravenous drug use, % any use in past 8 y</td>
<td>18.8</td>
<td>13.8</td>
<td>.60</td>
</tr>
<tr>
<td>Cocaine use, % any use in past 8 y</td>
<td>35.4</td>
<td>50.0</td>
<td>.14</td>
</tr>
<tr>
<td>Foreign travel, % in past 5 y</td>
<td>58.3</td>
<td>57.4</td>
<td>.94</td>
</tr>
</tbody>
</table>

* AIDS indicates the acquired immunodeficiency syndrome.
† Mantel-Haenszel χ².
‡ Mann-Whitney U test for two groups.
§ Six months prior to diagnosis (case patients) or enrollment (controls).

**RESULTS**

**Clinical Characteristics**

We identified five HIV-negative, immunocompetent BAP case patients, one HIV-negative, immunodeficient BAP case patient, and 42 HIV-positive BAP case patients. Surrogate interviews were necessary for 15 HIV-positive case patients enrolled early during the course of study (14 deceased and one with HIV dementia). The majority of the 48 case patients were San Francisco Bay Area residents at the time of BAP tissue diagnosis, with 15 patients (31%) receiving care from one of four University of California, San Francisco, hospitals and clinics and 15 (39%) receiving care from private San Francisco Bay Area hospitals and clinics. Of the remaining 15 case patients (31%), six lived in southern California, four in Texas, two in North Carolina, and one each in Florida, Maryland, and western Canada. Two controls were enrolled for each case with the exception of only one control being enrolled for two of the six HIV-negative case patients.

Among the 42 HIV-positive case patients, 14 (34%) had no prior diagnosis of the acquired immunodeficiency syndrome (AIDS), 19 (45%) had a prior AIDS diagnosis, and nine (21%) had a concomitant AIDS diagnosis within 1 month of the time of BAP tissue diagnosis. A prior history of intravenous drug use was reported by nine (21%) of the 42 HIV-positive case patients. All five HIV-negative, apparently immunocompetent case-patients were culture-negative for HIV-1 and had normal T-cell subsets. There were no significant differences among case patients (N=48) and controls (N=94) by personal characteristics, risk factors for HIV infection, history of an AIDS-defining illness (including Kaposi's sarcoma, Pneumocystis carinii pneumonia, toxoplasmosis, and so forth), recreational drug use, or foreign travel (Table 1).

**Environmental Exposures**

**Matched Analyses.**—Recent cat exposures were the only environmental exposures significantly associated with BAP disease (Table 2). In the matched univariate analysis, owning a cat (OR, 2.9; 95% confidence interval [CI], 1.4 to 5.8) and spending a minimum of 1 hour per day in contact with a cat (OR, 3.2; CI, 1.5 to 6.7) were associated with disease. Because several subjects had more than one cat, we evaluated differences in extent of exposure to the one cat with which the subject spent the most time (ie, the cat of most frequent exposure). There was a significant difference between case patients and controls in the amount of time spent with the cat of most frequent exposure (P<.001, Mann-Whitney U test for two groups). In addition, an increasing number of hours spent per day on average (<1, 1 to 8, >8 to 16, and >16) with the cat of most frequent exposure was associated with disease (P<.006, χ² test for trend).

Various types of contact with one or more cats, including a history of being recently licked by a cat (OR, 2.0; CI, 1.0 to 3.8), scratched by a cat (OR, 3.7; CI, 1.7 to 8.0), or bitten by a cat (OR, 3.9; CI, 1.8 to 8.9), were associated with disease in univariate analysis (Table 2). In addition, a history of a recent cat scratch that broke the skin (OR, 4.1; CI, 1.5 to 9.3) or a cat bite that broke the skin (OR, 2.9; CI, 1.2 to 7.1) was associated with disease. Changing the cat litter box and exposure to a cat outside the home were not associated with disease. While exposure to dogs was quite common, no dog or other pet exposures (excluding cats) were associated with having BAP. Exposure to plants, soil, water, and nonpet-related cutaneous trauma was not associated with disease.

**Detailed Cat Exposures.**—An addendum questionnaire further detailing household cat exposures was administered to 25 case patients and 54 matched controls. A matched univariate analysis of the data further supported an association between cat exposure and disease (Table 3). In addition, this analysis examined data on the age of household cats. Case patients were more likely than controls to have a kitten (a cat ≤1 year of age) living in the home (OR, 3.0; CI, 1.1 to 8.9). There was no association between sleeping with a household cat and disease.
Table 2.—Cat Exposures of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Patients (n=54)</th>
<th>Controls (n=37)</th>
<th>Odds Ratio (Matched)</th>
<th>Confidence Interval</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat ownership, %</td>
<td>66.7</td>
<td>39.9</td>
<td>2.9</td>
<td>1.4-5.8</td>
<td>.007</td>
</tr>
<tr>
<td>No. of cats owned, mean</td>
<td>1.1</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 h spent per day with a cat, %</td>
<td>64.6</td>
<td>34.0</td>
<td>3.2</td>
<td>1.5-6.7</td>
<td>.002</td>
</tr>
<tr>
<td>A cat scratch by ≤1 cats, %</td>
<td>62.5</td>
<td>30.9</td>
<td>3.7</td>
<td>1.7-8.0</td>
<td>.008</td>
</tr>
<tr>
<td>A cat scratch that broke the skin, %</td>
<td>56.3</td>
<td>26.6</td>
<td>4.1</td>
<td>1.8-9.3</td>
<td>.001</td>
</tr>
<tr>
<td>A cat bite by ≤1 cats, %</td>
<td>43.8</td>
<td>14.9</td>
<td>3.9</td>
<td>1.8-9.9</td>
<td>.001</td>
</tr>
<tr>
<td>A cat bite that broke the skin, %</td>
<td>25.0</td>
<td>9.6</td>
<td>2.9</td>
<td>1.2-7.1</td>
<td>.03</td>
</tr>
<tr>
<td>A cat or cat scratch by ≤1 cats, %</td>
<td>64.6</td>
<td>28.1</td>
<td>3.1</td>
<td>1.6-6.5</td>
<td>.003</td>
</tr>
<tr>
<td>A cat lick by ≤1 cats, %</td>
<td>50.0</td>
<td>30.9</td>
<td>2.0</td>
<td>1.0-3.8</td>
<td>.06</td>
</tr>
<tr>
<td>Change cat box at least once per month, %</td>
<td>31.3</td>
<td>26.6</td>
<td>1.3</td>
<td>0.6-2.7</td>
<td>.69</td>
</tr>
</tbody>
</table>

*Six months prior to diagnosis (case patients) or enrollment (controls).
†Mann-Whitney U test for two groups.

Insect Bite and Terrain Exposures.—Case patients (n=58) and matched controls (n=54) were asked about recent insect bites and terrain exposures. No association was found between insect bites (fleas, ticks, lice, chiggers or mites, mosquitoes, bedbugs, and bugs of unknown type) or exposure to various terrains (mountains, rivers, lakes, beaches, forests, deserts, and parks) and disease.

Analysis Excluding Surrogate Responses.—To eliminate possible bias resulting from the 15 surrogate interviews, a matched analysis was performed using only the data obtained from the 33 case patients who were interviewed directly. The associations between cat exposures and BAP disease were essentially unchanged. Cat ownership (OR, 2.8; CI, 1.0 to 7.5; P<.08) and a history of a recent cat scratch (OR, 4.3; CI, 1.5 to 12.7; P<.01), cat bite (OR, 3.9; CI, 1.3 to 11.6; P<.02), or a cat scratch or cat bite (OR, 3.4; CI, 1.2 to 10.0; P<.03) were associated with disease.

Unmatched Analyses

Cat Exposures Among Cat Owners.—When case patients (n=52) and controls (n=57) who owned cats were compared, case patients were more likely than controls to report a recent cat scratch (OR, 3.3; CI, 1.0 to 12.6; P<.04) or cat bite (OR, 3.5; CI, 1.1 to 10.8; P<.01), but not a cat lick (OR, 1.7; CI, 0.6 to 5.5; P<.28). The amount of time cat owners spent with household cats did not differ between case patients and controls (P>0.2). Mann-Whitney U test for two groups; overall median, 6 hours per day). Finally, among cat owners the number of household cats did not differ between case patients and controls (P>0.6, Mann-Whitney U test for two groups; overall median, two cats).

The addendum questionnaire was used to collect information on the age of cats (as many as three cats) living in the home of case patients (n=19) and controls (n=28). Among cat owners, the median age of all case-patient-owned cats (4 years) differed significantly from the median age (7.5 years) of control-owned cats (P<.03, Mann-Whitney U test for two groups). The median age of the youngest household cat (12 months) living with a case patient differed significantly from the median age of the youngest household cat (42 months) living with a control (P<.04, Mann-Whitney U test for two groups). Finally, among cat owners, case patients were more likely than controls to own a kitten (OR, 3.8; CI, 1.1 to 13.2; P<.002).

Cat Exposures Excluding Case Patients With Diagnosed CSD.—When specifically asked, five of the last 13 case patients enrolled for study were told of a possible relationship between CSD and their BAP illness. We compared exposures of the eight case patients not informed of a possible relationship with CSD with those of all 94 controls. Again, cat ownership (OR, 10.8; CI, 1.2 to 247.0; P<.01, two-tailed Fisher's Exact Test), and cat bite (OR, 9.5; CI, 1.7 to 59.0; P<.005, two-tailed Fisher's Exact Test) were associated with disease. These eight cases were also more likely than controls to have a history of recent cat lick or cat scratch, but these trends were not statistically significant (P<.08).

Bivariate Analyses

A matched bivariate analysis was conducted to assess confounding between the various cat exposure variables associated with BAP in the univariate analysis (Table 4). A history of a recent cat scratch (OR, 2.8; CI, 1.1 to 6.9) or cat bite (OR, 2.8; CI, 1.1 to 7.0) was associated with disease after controlling for cat ownership. In addition, a history of a recent cat scratch (OR, 2.4; CI, 1.0 to 5.8) or cat bite (OR, 2.3; CI, 0.9 to 5.8) was associated with disease after controlling for a recent cat bite or cat scratch, respectively. Cat ownership was not associated with disease after controlling for either a recent cat scratch or cat bite, and a history of a recent cat lick was not associated with BAP after controlling for cat ownership (Table 4).

Tissue Studies

An approximately 300–base pair 16S rDNA fragment was amplified from extracted DNA of all 22 case tissues tested. This fragment corresponded to the expected size of amplified product from Rochalimaea species or a closely related organism. The 300–base pair fragment was not amplified from the 22 control tissues (including 17 cutaneous lesions of Kaposi's sarcoma) or from DNA of the A. felis strain. All control tissues contained amplifiable DNA using β-globin primers.
COMMENT

In this study, we found that the newly described clinical syndrome of BAP was associated with a history of recent cat exposure. Exposure to cats has also been reported in patients with CSD.28,29 However, unlike conventional CSD, in which 87% to 99% of cases are reported anecdotally to follow recent cat contact,22,23 one third of the patients with BAP in our study had no known exposure to cats, suggesting that BAP may also be acquired from other sources.

On univariate analysis, several cat exposures were found to be risk factors for BAP disease, including cat ownership, an increasing amount of time spent per day (on average) with a cat, and a history of a cat lick, cat scratch, or cat bite. However, after controlling for cat ownership in the bivariate analysis, only having been recently bitten or scratched by a cat remained significantly associated with disease. This suggests that traumatic contact with a cat is associated with BAP disease. A matched analysis of detailed cat exposure data obtained from 28 case patients and 54 controls found that kitten exposure was associated with disease. In addition, an unmatched subanalysis of the data restricted to cat owners found exposure to younger cats (kittens in particular) to be a significant risk factor for disease. Among patients with classic CSD, 78% reported exposure to a kitten.22

Two hypotheses can be generated regarding the role of the domestic cat as a vector for the transmission of bacterial disease by a bite or scratch. The agent of BAP might be part of the normal flora of the feline oral cavity and pharynx, and therefore might be present on the pelage, claws, and teeth following grooming, allowing the transmission of these bacilli to humans by a bite or scratch. A second hypothesis, based on the close genealogical relationship of Rochalimaea species with agrobacteria and rhizobacteria,30 suggests that the agent of BAP might be a saprophytic plant or soil organism. Although this case-control study found no association between BAP and plant or soil exposures, it is possible that an infectious agent could be transmitted to humans following inoculation of human skin by the contaminated pelage, claw, or bite of a cat.

Several investigators have suggested that an unidentified arthropod vector may be responsible for the transmission of BAP bacilli, based on the association between other members of the family Rickettsiaceae and arthropod exposures, and a report of two patients with R. henselae bacteremia within 1 month following a tick bite.27 Because physical contact with a cat was a risk factor for BAP disease, we were particularly interested in insects that commonly infest cats. If cat fleas (or cat mites) harbor the bacilli responsible for BAP, and if cat flea (or cat mite) blood or feces were present on the claws, pelage, and teeth of cats, cats could inoculate these bacilli into human skin via a bite or scratch. Transmission experiments have clearly shown that R. quintana—infected house mite excrement is capable of infecting humans through abraded skin.32 Of interest, transovarial maintenance of a typhuslike Rickettsia in cat fleas has been described recently, but its relationship to the agent responsible for BAP has not been evaluated.33

In our study, subjects were queried in detail regarding bites from a variety of insects, including ticks, fleas, lice, mites, and mosquitoes, during the 1 year prior to enrollment. We found no association between insect bites and disease, but several methodologic issues may account for a failure to identify an association. These include (1) lack of power due to the small number of case patients interviewed about insect bites (n=28), (2) inability to obtain information on remote exposures (>1 year), and (3) failure to query subjects regarding insects commonly found in the home environment. Future studies should query cat owners about infestation of their cats(s) or home by insects.

To confirm that our case patients with a histologic diagnosis of BAP had infection with Rochalimaea or a closely related species, we performed the PCR on DNA extracted from available case-patient tissues. A DNA fragment of the expected size for Rochalimaea species18 was amplified from 16S rDNA extracted from infected tissues of 22 of our case patients. Although the PCR primers used to amplify DNA do not cross-react with A. felis, these primers do not distinguish among Rochalimaea species, B. bacilliformis, and Brucella abortus.16 However, infection with either of the latter two organisms was unlikely because Brucella abortus has not been reported outside South America,22 and B. abortus infection has not been associated with the histologic patterns of BAP.24

Our laboratory studies suggest that our case-patients were infected with Rochalimaea species or a closely related organism. Of interest, both R. henselae and R. quintana have recently been isolated from cutaneous BA lesions.18 Because BAP can be caused by either R. henselae or R. quintana, it is possible that risk factors for acquiring infection with these two organisms differ, providing an explanation for the one third of our case patients who gave no history of prior cat exposure. Finally, the PCR failed to amplify Rochalimaea species DNA from 17 cutaneous control tissue specimens of Kaposi’s sarcoma, providing evidence that cutaneous lesions of Kaposi’s sarcoma are not associated with Rochalimaea species infection, despite their vascular nature and similar clinical appearance.

Four potential sources of bias may have been present in this case-control study. First, one third of case patients were not interviewed directly (ie, surrogates provided information), whereas all controls were interviewed directly. However, a matched analysis excluding all 15 surrogate case patients found no substantial difference in any associations when compared with the overall matched analysis. Second, more than one third of case patients were interviewed more than 6 months after their BAP tissue diagnosis, thereby bringing into question the accuracy of their responses. Results of a matched analysis excluding these 21 case patients were unchanged. Third, case patients enrolled for study may have been given a diagnosis of CSD, which may have introduced recall bias. However, a recent history of cat ownership or cat bite remained a risk factor for disease in an unmatched analysis of the eight case patients never given a diagnosis of CSD (among the 13 queried) and all 94 controls. This suggests that recall bias was unlikely to be responsible for the association between traumatic cat exposures and BAP disease. Finally, physician-introduced suspicion bias may have been generated by soliciting a patient history of cat expo-

Table 4.—Bivariate Analysis for Cat Exposures of Study Participants

<table>
<thead>
<tr>
<th>Variable* (Adjusted by)</th>
<th>Odds Ratio (Matched)</th>
<th>Confidence Interval</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Own a cat (any cat bite)</td>
<td>1.7</td>
<td>0.7-3.9</td>
<td>.21</td>
</tr>
<tr>
<td>Any cat bite (own a cat)</td>
<td>2.8</td>
<td>1.1-7.0</td>
<td>.03</td>
</tr>
<tr>
<td>Own a cat (any cat scratch)</td>
<td>1.6</td>
<td>0.6-3.8</td>
<td>.33</td>
</tr>
<tr>
<td>Any cat scratch (own a cat)</td>
<td>2.8</td>
<td>1.1-6.9</td>
<td>.03</td>
</tr>
<tr>
<td>Own a cat (any cat lick)</td>
<td>2.5</td>
<td>1.0-5.9</td>
<td>.04</td>
</tr>
<tr>
<td>Any cat lick (own a cat)</td>
<td>1.2</td>
<td>0.5-2.8</td>
<td>.69</td>
</tr>
</tbody>
</table>

*Six months prior to diagnosis (case patients) or enrollment (controls).
†Mantel-Haenszel χ²

at (among the 13 queried) and all 94 controls. This suggests that recall bias was unlikely to be responsible for the association between traumatic cat exposures and BAP disease. Finally, physician-introduced suspicion bias may have been generated by soliciting a patient history of cat explo-
ure. This fourth potential bias is un-
likely because (1) all 48 case patients
were as of the identification of uninfected path-
2. Staber LN, Welch DF, Hanss D, Cooy DW. A
recently recognized fastidious gram-nega-
1990;322:1567-1573.
3. Regner BL, Anderson BE, Chaffard DE, III,
Rodriguez AM, Mc Jones DC, Carr JJ. Char-
acterization of a novel Rochalimaea species, *R.
heselae*, sp. nov., isolated from a blood of a febrile, human
4. Welch DF, Pickett DA, Stiner LG, Steigerwalt AG,
Brenner DJ, Rochalimaea *heselae*, sp. nov.,
a cause of septicaemia, bacillary angiomatosis, and
5. English CK, Wear DJ, Marglethe AM, Lissner CR,
Wash GP. Cat-scratch disease: isolation and
6. Tappero JW, Koehler JE. Cat-scratch disease and
7. Chan JKC, Lewin KJ, Lombard CM, Teitelbaum S,
Dorffman RF. Histopathology of bacillary angio-
8. Spach DI, Panther LA, Thornier DR, Dunn JE,
Porl JE, Miller RA. Intrahepatic bacillary angiomato-
Sis in a patient infected with human immuno-
ical and pathological features of bacillary peliosis
hepatis in association with human immunodefi-
10. Kemper CA, Lombard CM, Direrenski SC,
Tomkins LS. Visceral bacillary epithelioid angio-
11. Knion DJ, Quinn FD, Bergier TG, LeBoit PE, Tappero JW. Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angio-
12. Relman DA, Loutit JS, Schmidt TM, Fallows S,
Tomkins LS. The agent of bacillary angiomatosis: an approach to the identification of uninfected path-
13. Staber LN, Welch DF, Hanss D, Cooy DW. A
recently recognized fastidious gram-negative patho-
1990;322:1567-1573.
14. Regner BL, Anderson BE, Chaffard DE, III,
Rodriguez AM, Mc Jones DC, Carr JJ. Character-
ization of a novel Rochalimaea species, *R.
heselae*, sp. nov., isolated from a blood of a febrile, human
15. Welch DF, Pickett DA, Stiner LG, Steigerwalt AG,
Brenner DJ, Rochalimaea *heselae*, sp. nov.,
a cause of septicaemia, bacillary angiomatosis, and
16. English CK, Wear DJ, Marglethe AM, Lissner CR,
Wash GP. Cat-scratch disease: isolation and
17. O'Connor SP, Morsch M, Steigerwalt AG, Bren-
er DJ, Stackerbehardt E. 16S rRNA sequences of
*Bartonella bacilliformis* and cat-scratch disease bacilli reveal close relationship with alpha-
osal of *Afipia* gen. nov., with *Afipia felis* sp. nov. (formerly the cat-scratch disease bacillus), *Afipia
clevelandensis* sp. nov. (formerly the Cleveland Clinic
Foundation strain), *Afipia brovenae* sp. nov., and three unnamed genospecies. J Clin Microbiol.
19. Relman DA, Lepp FW, Sallier KN, Schmidt TM. Phylogenetic relationships among the agent of
21. Carrión HH. Cat-scratch disease: an overview
based on a study of 1,200 patients. AJDC. 1955;11:1124-1123.
national Conference on AIDS, Florence, Italy, June 16-21, 1991. Rome, Italy: Istituto Superiore di San-
23. Dean AD, Dean JA, Burton JH, Dicker RC.